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Attorney Docket No.: **PENN-0749**
Inventors: **Muzykantov et al.**
Serial No.: **09/762,023**
Filing Date: **June 28, 2001**
Page 4

REMARKS

Claims 5 and 9 are pending in the instant application. Claims 5 and 9 have been rejected. Claim 5 has been canceled. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claim 5 under 35 U.S.C. § 112, first paragraph
- Written Description

The rejection of claim 5 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time application was filed, had possession of the claimed invention has been maintained.

Applicants respectfully traverse this rejection.

However, in an earnest effort to advance the prosecution of this case, Applicants have canceled claim 5.

Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claim 5 under 35 U.S.C. § 112, first paragraph
- Lack of Enablement

Claim 5 has been rejected under 35 U.S.C. § 112, first

Attorney Docket No.: PENN-0749
Inventors: Muzykantov et al.
Serial No.: 09/762,023
Filing Date: June 28, 2001
Page 5

paragraph for lack of enablement. The Examiner has acknowledged the specification to be enabling for dissolution of fibrin clots by administering a non-internalizable antibody to ICAM-1 and a fibrinolytic or anti-coagulant. However, the Examiner suggests that the specification does not reasonably provide enablement for a method of dissolving of intravascular blood clots in the pulmonary vasculature of an animal comprising intravenously administering to the animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds any antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cell.

Applicants respectfully traverse this rejection.

However, in an earnest effort to advance the prosecution of this case, Applicants have canceled claim 5.

Withdrawal of this rejection is therefore respectfully requested.

III. Rejection of Claims 5 and 9 under 35 U.S.C. § 103(a)

Claims 5 and 9 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Bowes et al. (Neurology 1995) in view of Imaizumi (Transpl. Proc. 1994), Mulligan et al. (Amer. J. Pathol. 1993) and Panes (Amer. J. Physiol. 1995), and further in view of Runge et al. and Torchilin et al. and Muzykantov et

Attorney Docket No.: PENN-0749
Inventors: Muzykantov et al.
Serial No.: 09/762,023
Filing Date: June 28, 2001
Page 6

al. (BBA 1986), and Muzykantov et al. (Amer. J. Physiol. 1996). Applicants' arguments presented in the last response were not found convincing as the Examiner suggests that given the teachings of Mulligan et al. that anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, it would have been immediately apparent to one skilled in the art that the antibody is non-internalizable.

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner's suggestion that experiments by Mulligan et al. relating to accumulation in the pulmonary vasculature are indicative in any way of internalization or lack of internalization of an antibody into endothelial cells. The experiments of Mulligan et al. measured labeled antibody in selected tissues. These experiments in no way provided information as to whether the label was inside or outside the cell.

Further, regardless of whether Mulligan is suggestive of the antibody being non-internalized, the combination of references still provides no reasonable expectation that a fibrinolytic or anticoagulant agent, when conjugated to a non-internalized antibody would remain therapeutically active for prolonged

Attorney Docket No.: PENN-0749
Inventors: Muzykantov et al.
Serial No.: 09/762,023
Filing Date: June 28, 2001
Page 7

periods in the lumen, particularly when it was well known in the art that anticoagulants and fibrinolytics undergo inactivation and elimination in the bloodstream. See page 1, lines 16-17 of the instant specification.

MPEP § 2143.01 is clear; the test for obviousness is what the combined teachings of the reference would have suggested to one of ordinary skill in the art, and all (emphasis added) teachings in the prior art must be considered to the extent that they are in analogous arts. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See MPEP § 2143.01 and *In re Mills* 16 USPQ2d 1430 (Fed. Cir. 1990).

The prior art, when viewed as a whole, is clearly not suggestive of the desirability of a conjugate of a non-internalizable antibody to ICAM-1 to an anti-thrombotic agent which prolongs length of time of the anti-thrombotic agent in the bloodstream when stability of the anti-thrombotic agent in the bloodstream was a well-established problem.

Further, the prior art, when viewed as a whole, clearly provides no reasonable expectation of success as required by MPEP § 2143.02 that a conjugate of a non-internalizable antibody to

Attorney Docket No.: PENN-0749
Inventors: Muzykantov et al.
Serial No.: 09/762,023
Filing Date: June 28, 2001
Page 8

ICAM-1 to an anti-thrombotic agent will remain active when maintained for prolonged periods in the bloodstream, an area where stability of such agents is problematic.

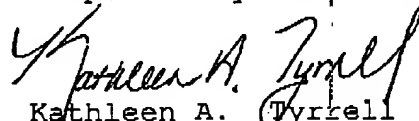
Thus, the cited prior art combination cannot render the instant invention obvious.

Withdrawal of this rejection under 35 U.S.C. § 103(a) is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,


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